

10/10/2015 Part II Immunology option lecture notes: **Intracellular nucleic acid sensing**

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- The innate immune system can detect and respond to both foreign and self nucleic acids. Note that self-DNA is normally compartmentalised in the nucleus and mitochondria and under normal conditions is rapidly degraded when found outside this location.
- Pathogens, especially viruses, but also some bacteria and parasites, expose their genomes inside cells and this an important target for the host innate immune response.
- Nucleic acid detection is crucial for the initial rapid induction of inflammation and the interferon response against virus infection.
- When nucleic acid sensing machinery fails to function correctly this leads to susceptibility to infection but when they are not cleared efficiently this leads to autoimmune disease
- Four different signalling pathways are currently defined.
 1. Toll-like receptor and MyD88 dependent detection of RNA/DNA
 2. AIM-2 dependent inflammasome activation
 3. Intracellular activation of IPS1- or STING- dependent signalling
 4. Intracellular activation of NF- κ B signalling
- Intracellular RNA sensors are well defined and their molecular mechanisms will be discussed in the lecture. The identity of the intracellular 'DNA sensors' is more controversial. The best current evidence exists for cGAS, DNA-PK and IFI16.
- cGAS is homologous to 2'-5' oligoadenylate synthetase. These enzymes bind to nucleic acids and produce cyclic-dinucleotide second messengers which subsequently activate innate immune signalling pathways. In the case of cGAS, cGAMP is produced which binds and activates STING resulting in expression of IRF3-dependent genes.
- DNA-PK is normally involved in DNA repair in the nucleus, but also exists in the cytoplasm where it can detect viral DNA, such as that of vaccinia virus. Vaccinia virus in turn, makes a protein which binds DNA-PK and inhibits its activity in the cytoplasm.

References:

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